Risk of Venous Thromboembolism and Short-Term Exposure of Anti-Diabetic Treatment in Diabetic Population: A Nested Case-Control Study

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Background: Venous thromboembolism (VTE) is a cardiovascular condition that occurs when a thrombus (or blood clot) forms in the veins. A common risk factor in the development of VTE is diabetes, due to the proinflammatory and prothrombotic nature of the disease. It has previously been suggested that anti-diabetic treatment in patients with type 2 diabetes may reduce their risk of VTE. However, the evidence is not easily comparable and inconsistent as most of them only look at one or two anti-diabetic medications.

Objective: This study therefore sought to investigate the risk of VTE in patients with type 2 diabetes when exposed to the following categories of anti-diabetic medication: alpha glucosidase inhibitors, biguanides, dipeptidyl peptidase 4 (DPP-4) inhibitors or sulfonylureas.

Methods: A nested-case control study design was used with data from an electronic health database simulated from the French national administrative database SNDS (National System for Health Data). Outcome was defined as having a diagnosis of VTE (main or associated), a record of at least one VTE procedure, or a record of at least one prescription of low-molecular-weight heparin for therapeutic use in the period from 2017 to 2020. Exposure was defined as at least one prescription of any of the following anti-diabetic medication categories at any time from 2018 to 2020: alpha glucosidase inhibitors, biguanides, dipeptidyl peptidase 4 (DPP-4) inhibitors or sulfonylureas. Cases were individually matched to three controls on sex, age, history of cancer, hypertension, COPD, fractures, and major surgery.

Analysis: A multivariate conditional logistic regression model was fitted to calculate odds ratios (ORs) for VTE associated with antidiabetic medication use, matched and adjusted on variables mentioned previously. Sensitivity analysis looked at the association if outcome definition was changed to only having at least one prescription of low-molecular-weight heparin in the period from 2018 to 2020.

Results: Use of biguanides was associated with a higher odds of VTE after multiple adjustments (OR 1.21 (95% CI: 1.08-1.36)), while use of alpha glucosidase inhibitors and sulfonylureas were associated with lower odds of VTE (OR 0.37 (95% CI: 0.09-1.07) and OR 0.69 (95% CI: 0.55-0.87) respectively). Use of DPP-4 inhibitors was inconclusive on the odds of experiencing VTE (OR 1.01 (95% CI: 0.51-1.88)).

Conclusion: Use of biguanides was associated with higher odds of VTE, while use of alpha glucosidase inhibitors and sulfonylureas was associated with lower odds of VTE. Use of DPP-4 inhibitors was not associated with higher or lower odds of VTE. Future studies are needed to confirm whether these anti-diabetic medications have a protective or harmful effect on the risk of VTE, as well as determining if these results are present in the general population.

Introduction

Venous thromboembolism (VTE) is a condition that occurs when a thrombus (or blood clot) forms in the veins. Interrelated conditions include deep vein thrombosis (DVT), where a thrombus forms in the deep veins of the body, and pulmonary embolism, a sudden blockage in the pulmonary arteries. Although VTE is preventable, it is among the most common vascular diseases in most countries[1] and is associated with high morbidity and mortality.

VTE can be diagnosed with ultrasonography or contrast venography imaging techniques, as well as blood tests such as the D-dimer test to assess for blood clots. When diagnosed, VTE can be treated with different treatments and procedures depending on the type of VTE, severity and characteristics of the patient. Most commonly, it is treated with curative low-molecular-weight heparin, an oral anticoagulant medication to reduce the ability of the blood to clot; in more severe cases, inferior vena cava filters can be used in DVT capture a clot in the deep vein vasculature, or surgical procedures such as a thrombectomy or embolectomy can be undertaken.[2]

Commonly cited risk factors for VTE include obesity, hypertension, dyslipidemia, smoking and diabetes.[3] Diabetes in particular has been linked to an increased risk of developing VTE, although evidence has been inconsistent. Diabetes mellitus is a metabolic condition resulting from defects in insulin secretion, action, or occasionally both. Prolonged exposure to hyperglycemia leads to diverse proinflammatory effects associated with endothelial and vascular smooth muscle dysfunction, and induces a prothrombotic state via alterations in platelet aggregation.[4] Previous epidemiological studies have shown patients with diabetes are more at risk of developing DVT and pulmonary embolism, and that the relative risk of VTE is higher in younger patients with diabetes.[5] Increased generation of thrombin and a higher concentration of procoagulant cell-derived circulating microparticles in patients with type 2 diabetes is thought to encourage hypercoagulability and play a potential pathogenic role in the increased risk of VTE in these patients.[6]

Anti-diabetic treatments have also been previously hypothesized to protect against VTE. For instance, metformin, an antiglycemic agent and common treatment for type 2 diabetes, is thought to decrease activation, adhesiveness, and aggregation of platelets[6], which may have a beneficial anticoagulant effect that prevents VTE development. Furthermore, there is some evidence of the effect of some anti-diabetic drugs on risk of VTE in diabetic populations. For example, previous studies have shown that metformin has a protective effect on the risk of VTE in type 2 diabetes patients [7], while DPP-4 inhibitors were shown to be associated with an increased risk of VTE in diabetic patients [8] and sulfonylureas and glitazones were not associated with an increased or decreased risk of VTE in diabetic patients [8]. However, the evidence is

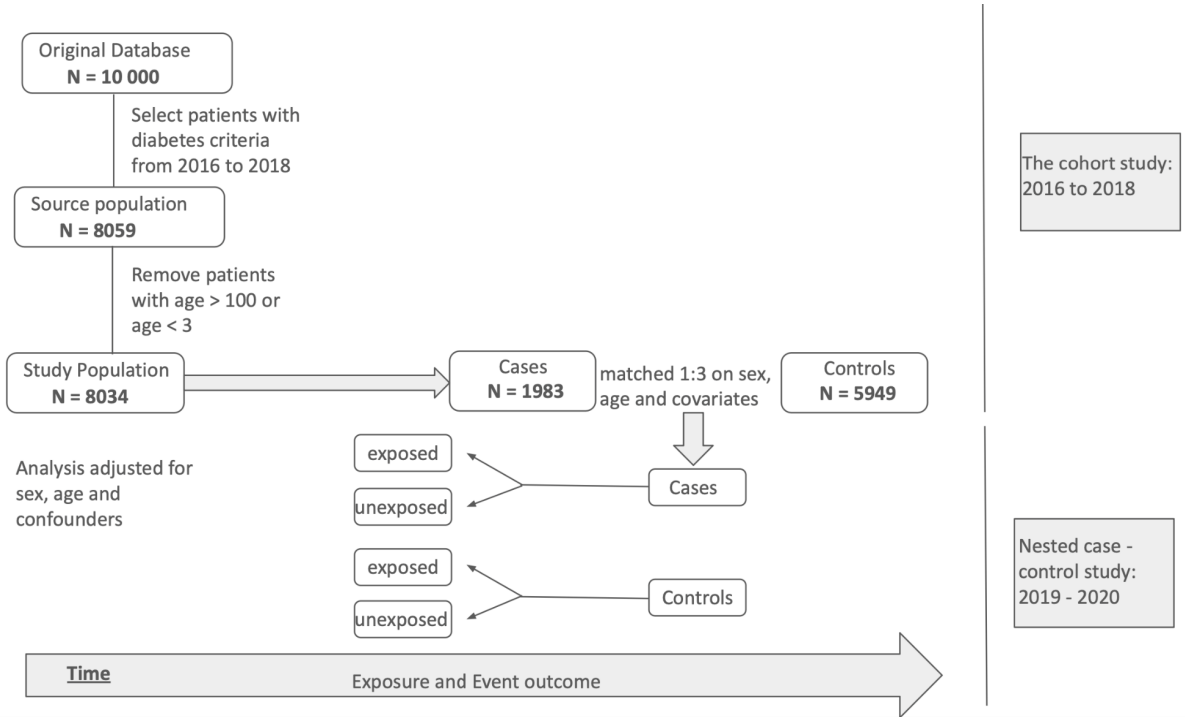
not easily comparable and inconsistent as most of them only look at one or two anti-diabetic medications, and the association between exposure to different types of anti-diabetic drugs and risk of VTE among type 2 diabetes mellitus patients is not well understood. Understanding the effect of anti-diabetic drugs on risk of VTE in diabetic patients can help inform treatment guidelines for VTE in patients with type 2 diabetes mellitus. This study thus investigates the risk of venous thromboembolism according to exposure to many types of anti-diabetic treatments among people with type 2 diabetes mellitus.

Methods

Study design

The study used a nested case-control design to estimate risk of VTE stratified by antidiabetic treatment among a type 2 diabetes mellitus cohort from an electronic health database based on the French national administrative database SNDS (National System for Health Data). The diabetic cohort was defined as patients who had either a long-term illness diagnosis of type 2 diabetes mellitus, a recorded associated diagnosis of hospitalization of type 2 diabetes mellitus, a main diagnosis of hospitalization of Type 2 diabetes mellitus, or at least three prescriptions of any anti-diabetic drugs in the period from 2016 to 2018. This timeframe was chosen to ensure there is time for those patients with diabetes to have taken anti-diabetic drugs when estimating the risk of VTE. Cases were selected from the cohort of diabetics who had the outcome (VTE) between 2019 and 2020 and individually matched on sex and age and covariates cancer, COPD, hypertension, fracture and surgery (cardiothoracic, abdominal, pelvic or orthopedic) to three controls selected in the same period. Cases and controls were then assessed for their exposure to the following categories of anti-diabetic drugs: biguanides, sulfonylureas, alpha glucosidase inhibitors and DDP-4 inhibitors. Figure 1 shows the key aspects of the study design.

Figure 1. Flow chart of the study design.



Setting

The study was based on a database modeled on the Hospital Information System in use at the "Centre Hospitalier Universitaire" of Bordeaux-Pellegrin. This electronic health database contains data on hospitalizations, drug prescriptions, drugs biology, in-hospital and out-of-hospital medical or surgical procedures, long-term illness and associated diagnosis of patients, as well as anonymized patient information from patients who were hospitalized at the the "Centre Hospitalier Universitaire" of Bordeaux-Pellegrin from April 20th, 2016 to December 31st, 2020. For confidentiality purposes, the data is simulated following the general distribution of the data found in the hospital, and follows the design of the French Système National des Données de Santé (SNDS). Based on the Redsiam criteria for diabetes [13], patients from the database were recruited in the cohort (source population) if they had a long-term illness diagnosis of Type 2 diabetes mellitus, a recorded associated diagnosis of hospitalization of Type 2 diabetes mellitus, a principal diagnosis of hospitalization of Type 2 diabetes mellitus, or at least three prescriptions of any anti-diabetic drugs in the period from 2016 to 2018 in the electronic health database. The source population was queried from the electronic health database using the above criteria in DBeaver using SQL language. The 10th edition of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes were used for the diagnosis criteria (ICD-10 code beginning with E11 for type 2 diabetes mellitus) while the Anatomical Therapeutic Chemical (ATC) classification was used for the anti-diabetic drug prescription criteria (ATC code beginning with A10A for

insulin, A10B for Blood Glucose Lowering Drugs excl. Insulin and excluding ATC code A10BX06, benfluorex) (Appendix 1). Patients were then followed from 2019 to 2020 and assessed for their exposure status and outcome from the electronic health database. Age, sex, and confounders (history of cancer, chronic obstructive pulmonary disease (COPD), hypertension, fracture or history of cardiothoracic, abdominal, pelvic or orthopedic surgery) data was also collected in the electronic health database.

Participants

Among the cohort of diabetics (source population), individuals older than 100 or under the age of 3 were excluded (toddlers and babies). Ages above 100 were assumed to be measurement error, and individuals under 3 (considered toddlers or babies) should receive tailored treatment to individual patient characteristics [9]. Then, the study population was defined as the cases (individuals who experienced at least one VTE event) and controls (individuals who did not experience an event of VTE) selected from the cohort in the period from 2018 to 2020. Cases were selected from the cohort of diabetics who had at least once the outcome (VTE) between 2018 and 2020 and were individually matched without replacement on sex, nearest age, and history of confounders (from 2016 to 2018: cancer (any), chronic obstructive pulmonary disease (COPD), fracture (any), hypertension and cardiothoracic, abdominal, pelvic or orthopedic surgery) to three controls selected between 2018 to 2020. The ratio of matching was decided based on similar previous studies [9,14]. For control sampling, the sampling date was decided as the date of the patient with VTE (case) that was matched to those controls. Unmatched controls will be dropped from the analysis. If there are cases without eligible controls, the matching criteria will be loosened to include 5 year bands for age.

Variables

Exposure

The exposures of interest were the following anti-diabetic drugs categories: biguanides, sulfonylureas, alpha glucosidase inhibitors and DDP-4 inhibitors. The anti-diabetic drug categories were defined from the the Anatomical Therapeutic Chemical (ATC) classification as ATC code beginning with A10BA (Biguanides), A10BB (Sulfonylureas), A10BH (DPP-4 Inhibitors) and A10BF (Alpha-glucosidase Inhibitors) (Appendix 1). Any route of administration was considered. The exposed patients were first queried from the source population in DBeaver using SQL language just looking at the ATC codes without looking at temporality (if exposure was before the outcome). A patient was defined as exposed if they had at least one prescription of any of the anti-diabetic drug category at any time from 2018 to 2020 without looking

at temporality (if the exposure happened before the outcome). Then, an exposure status variable was made in R for each anti-diabetic drug category where a patient was defined as exposed if they have taken this drug at least once and if their date of exposure (date of prescription) precedes the date of outcome (date of VTE). If a patient had repeated exposures of the same drug in the time period, they were considered as different patients. If a patient had exposure to multiple drugs in the time period, they were also considered as different patients. For patients without the outcome (controls), sampling date as described above was used. Therefore, a case or control was defined as exposed for each anti-diabetic drug category if they had at least one prescription of this anti-diabetic drug category at any time from 2018 to being sampled as a case or control (date of VTE or date of sampling). A case or control was therefore considered unexposed for each anti-diabetic drug category if they did not meet the above criteria.

Outcome

A diabetic patient was considered as a case if they had the outcome, defined as having a main reason for hospitalization due to VTE, an associated diagnosis of hospitalization of VTE, having a record of at least one VTE surgical procedure or having a record of at least one prescription of low-molecular-weight heparin in the period from 2018 to 2020. Heparin could be given at low dose (under 5000UI)[10,11] as prevention for VTE or at high dose for therapeutic usage. To be considered as an indicator of the outcome, only the therapeutic (treatment) prescriptions were considered in the definition of the outcome. The most common VTE surgical procedures are venous thrombectomy and venous thrombolysis[2], conducted in a hospital setting only. They were also included in the definition of the outcome. Date of the outcome was defined as the date when the patient was hospitalized for VTE, on the assumption that the associated diagnosis and the procedure is tied to the hospitalization date of entry. A diabetic patient in the cohort will be considered a case if they have at least one recorded event of the outcome between 2018 and 2020. All events for every patient were included in the analyses and considered as distinct patients. From this definition, the patient population with the outcome was queried from the source population in DBeaver using SQL language. The ICD-10 codes were used for the diagnosis criteria (ICD-10 codes beginning with I26 - Pulmonary Embolism, I80 - Phlebitis and thrombophlebitis or I82 - Other venous embolism or thrombosis), the Classification Commune des Actes Médicaux (CCAM)[12] was used for the surgical procedures (CCAM code beginning with DHNF001 - Venous Thrombolysis or EGFA004 - Venous Thrombectomy), and the Anatomical Therapeutic Chemical (ATC)[12] classification was used for the low-molecular-weight heparin (ATC code beginning with B01AB - Low-molecular-weight Heparin) (Appendix 1). We exclude heparin drugs by the trade name Lovenox 2%, INNOHEP 4%, INNOHEP 3%, and INNOHEP 2%, which have much smaller dosages and are used in

prophylaxis of VTE. [13]

Covariates

Confounders of interest in this analysis included age, sex, and comorbidities such as history of fractures, hypertension, cancer, chronic obstructive pulmonary disease (COPD) and surgery [8.] These confounders were selected based on various reasons. Age and sex are included as risk of VTE varies across the lifespan[13], and VTE has been shown to be more common in women[7]. Taking antidiabetic medication is also not uniform across age and sex [15]. Risk of fractures, including traumatic or pathological fracture involving upper or lower limbs, spine or pelvis, are known to be common in patients taking antidiabetic treatment[16], and having a fracture also elevates the risk of VTE. [17] Similarly, hypertension [18], cancer [19] and COPD (20) are common risk factors for VTE and are conditions closely associated with diabetes.[21–23]. Risk of VTE is also known to be elevated after major surgery, especially of cardiothoracic, abdominal, pelvic or orthopedic surgery [24], and patients with diabetes are more likely to have postsurgical complications [14] . Age was defined as the difference between the date of diabetes diagnosis (either the hospitalization start date, the long term disease start date, or anti-diabetic drug prescription) and the patient's birth date. Sex was provided in the electronic health database. The ICD-10 codes were used for the fracture, hypertension, cancer, chronic obstructive pulmonary disease (COPD) and surgery confounders (see Appendix 1 for codes).

Statistical Analysis

A multivariate conditional logistic regression was performed on the matched dataset and adjusted on the confounders mentioned above. Goodness of fit was verified with the Area Under the Curve (AUC) metric. Model selection was done using the Bayesian Information Criterion (BIC)[25]. After noticing the lack of patients from the source population who had a main reason for hospitalization due to VTE or had a record of at least one VTE surgical procedure (making the outcome defined only as having an associated diagnosis of hospitalization of VTE or having at least one prescription of low-molecular-weight heparin in the period from 2018 to 2020), a sensitivity analysis was performed to estimate the risk of VTE if the outcome definition was changed to only having at least one prescription of low-molecular-weight heparin in the period from 2018 to 2020. The analyses were performed as intention-to-treat analyses, regardless of whether the participants actually took the prescribed drugs. Statistical analysis was done using R version 4.3.2 [26], with matching done with the package MatchIt [27]

Results

After matching, the study population consisted of a total of 7932 patients, divided into 1983 cases and 5949 controls. Median age was 67 (IQR 57, 76). Cases were more often older and showed a higher prevalence of comorbidities such as history of cancer, COPD, fractures, hypertension and surgeries compared to controls (Table 1). Overall, 850 (43%) of cases and 2393 (40%) of controls were taking an antidiabetic medication. Use of biguanides and DPP-4 inhibitors was associated with higher odds of experiencing VTE in the unadjusted matched model (OR 1.29 (95% CI: 1.16-1.44), p-value <0.001 and OR 1.16 (95% CI: 0.60-2.09), p-value 0.6 respectively), whereas use of alpha glucosidase inhibitors and sulfonylureas was associated with lower odds of experiencing VTE (OR 0.29 (95% CI: 0.07-0.82), p-value 0.043 and OR 0.59 (95% CI: 0.47-0.74), p-value <0.001 respectively). After adjusting on the variables used in the matching (age, sex, history of cancer, COPD, hypertension, fracture and surgery), use of biguanides remained associated with higher odds of VTE (OR 1.21 (95% CI: 1.08-1.36), p-value <0.001), while use of DPP-4 became inconclusive (OR 1.01 (95% CI: 0.51-1.88), p-value >0.9). Use of alpha glucosidase inhibitors and sulfonylureas also remained associated with lower odds of VTE after model adjustment (OR 0.37 (95% CI: 0.09-1.07), p-value 0.11 and OR 0.69 (95% CI: 0.55-0.87), p-value 0.002 respectively) (Table 2). A sensitivity analysis was performed to investigate whether altering the outcome definition for VTE may influence the odds ratios obtained. The results of the sensitivity analysis are shown in Appendix 2. Overall, changing the outcome definition did not significantly alter the ORs, with the exception of DPP-4, which under the new outcome definition showed a slightly protective effect against experiencing VTE (OR 0.88 (95% CI: 0.44, 1.65)), although still statistically insignificant at p-value=0.7.

Table 1. Demographic and clinical characteristics of the study population (patients with type 2 diabetes mellitus).

Characteristic	**Overall**, N = 7,932[1]	**Cases**, N = 1,983[1]	**Controls**, N = 5,949[1]
Sex			
1	4,713 (59%)	1,213 (61%)	3,500 (59%)
2	3,219 (41%)	770 (39%)	2,449 (41%)
Age	67 (57, 76)	70 (61, 78)	66 (55, 75)
Cancer			
0	6,803 (86%)	1,515 (76%)	5,288 (89%)
1	1,129 (14%)	468 (24%)	661 (11%)
COPD			
0	7,516 (95%)	1,816 (92%)	5,700 (96%)
1	416 (5.2%)	167 (8.4%)	249 (4.2%)
Fracture			
0	7,844 (99%)	1,944 (98%)	5,900 (99%)
1	88 (1.1%)	39 (2.0%)	49 (0.8%)
Hypertension			
0	6,153 (78%)	1,273 (64%)	4,880 (82%)
1	1,779 (22%)	710 (36%)	1,069 (18%)
Surgery			
0	7,253 (91%)	1,698 (86%)	5,555 (93%)
1	679 (8.6%)	285 (14%)	394 (6.6%)
Biguanides			
0	5,425 (68%)	1,253 (63%)	4,172 (70%)
1	2,507 (32%)	730 (37%)	1,777 (30%)
Sulfonylureas			
0	7,283 (92%)	1,880 (95%)	5,403 (91%)
1	649 (8.2%)	103 (5.2%)	546 (9.2%)
Dipeptidyl peptidase 4 (DPP-4) inhibitors			
0	7,880 (99%)	1,969 (99%)	5,911 (99%)
1	52 (0.7%)	14 (0.7%)	38 (0.6%)
Alpha glucosidase inhibitors			
0	7,897 (100%)	1,980 (100%)	5,917 (99%)
1	35 (0.4%)	3 (0.2%)	32 (0.5%)

[1] n (%); Median (IQR)

Table 2. Crude and adjusted ORs of VTE associated with use of different classes of anti-diabetic medication.

	Matched & Crude Model			Matched & Adjusted Model*		
Antidiabetic Medication	**OR**[1]	**95% CI**[1]	**p-value**	**OR**[1]	**95% CI**[1]	**p-value**
Biguanides						
0	—	—		—	—	
1	1.29	1.16, 1.44	<0.001	1.21	1.08, 1.36	<0.001
Alpha glucosidase inhibitors						
0	—	—		—	—	
1	0.29	0.07, 0.82	0.043	0.37	0.09, 1.07	0.11
Dipeptidyl peptidase 4 (DPP-4) inhibitors						
0	—	—		—	—	
1	1.16	0.60, 2.09	0.6	1.01	0.51, 1.88	>0.9
Sulfonylureas						
0	—	—		—	—	
1	0.59	0.47, 0.74	<0.001	0.69	0.55, 0.87	0.002

[1] OR = Odds Ratio, CI = Confidence Interval

*Adjusted on matching variables of age, sex, cancer, COPD, hypertension, fracture, and surgery.

Discussion

In this nested case-control study, the results indicate that use of at least one alpha glucosidase inhibitor has the biggest decrease on the odds of experiencing a VTE event compared to not using this antidiabetic medication, with the matched and adjusting model showing a 63% decrease (although statistically insignificant), followed by sulfonylureas with a 31% decrease in the odds of experiencing a VTE event compared to not using this anti-diabetic drug (statistically significant). In contrast, the use of at least one biguanide was associated with a 21% increase in the odds of experiencing a VTE event compared to not using this anti-diabetic drug (statistically insignificant), and the use of at least one DPP-4 inhibitor seems to not increase or decrease the odds of experiencing a VTE event compared to not using this anti-diabetic drug (statistically significant). When looking at the statistically significant results for the matched and adjusted results (alpha-glucosidase inhibitors and DPP-4 inhibitors), the confidence intervals are increasingly large and include the null, indicating imprecision in the effect measure. Some of these results also contradict previous studies with a similar objective of assessing the risk of venous thromboembolism according to exposure to certain types of antidiabetic treatments among people with type 2 diabetes mellitus. Previous cohort studies demonstrated a protective effect of metformin (most

commonly used biguanide for type 2 diabetics) on VTE risk [6, 9], while DPP-4 was also shown to increase the risk of VTE [7, 28] or have no difference on the risk of VTE [29].

Due to the short time period for looking at exposures, each patient was only exposed once to a drug. There are also no patients who were exposed to multiple drugs. Thus, this study was not able to look at cumulative exposures from repeated exposure to one drug or to different drugs. Furthermore, our study also assumes full treatment adherence, but this may vary depending on the drug administration method. Antidiabetic treatments have been found to have low treatment adherence, being lowest with oral drugs such as biguanides [30]. Lower treatment adherence for certain oral drugs such as biguanide compared to alpha glucosidase inhibitors and sulfonylureas may explain different odds of VTE in our study compared to previous studies . However previous studies haven't found metformin to have a significantly lower treatment adherence compared to other oral antidiabetic drugs [31].

This study made large assumptions when defining the exposure status variable, such as not looking at how long before the outcome was compared to the exposure. We made the assumption that any exposure before the outcome could have caused the outcome, without looking at temporality. In reality, there would be a delay between intake of the drug (or prescription of the drug) and potential VTE event which would mean exposures that are close to the outcome date would not be considered.Our results include those exposed patients who don't have the delay time between exposure and outcome, therefore our effect estimate is potentially inflated. Looking at time-to-event would have been interesting to do to better estimate the effect of anti-diabetic drugs on VTE.

The nested case-control study design also potentially introduced biases. This study attempted to account for the most common confounders influencing the association between antidiabetic medication and VTE and which were also available in the administrative database by matching for them. However, in case-control, matching ensures that the distributions of the confounders are similar across outcome groups (cases and controls), not across exposure groups. Matching is intended to reduce confounding, but the main benefit is to improve efficiency and study precision. In fact, it actually potentially introduces a type of selection bias called "selection confounding". Matching makes the matching variables independent of the outcome, apparently removing confounding. But, assuming there are no other confounders, a factor associated with exposure needs to be independent of disease conditional on the exposure to ensure that it does not produce additional confounding. If there is confounding in the source population (or in this study unmeasured confounders such as other comorbidities), the matching-created selection bias will be superimposed to the initial confounding in the estimated OR. Adjustment for the matching variables was performed to mitigate this bias, but it is very likely that there is residual bias in this study's effect measures [32,33]. Also, due to the high number of matching variables in this study making the cases and controls increasingly similar with respect to the exposures, it is very likely that there is

overmatching, especially if the matching variables are correlated together or if the matched variable is weakly or not associated with the outcome but strongly with the exposure [33].

Furthermore, by matching, the sample of controls is no longer representative of the source population. Selecting from our database population (hospitalized patients) made generalization to the out-of-hospital population difficult. For instance, our data source contains 10 000 cases, 80.59 % fitting our criteria for diabetes, when diabetes only concerns 5.3 % of the population in France in 2020 [34]. Another potential source of bias is information bias regarding the outcome definition, the choice of heparin drugs for prophylaxis, and those used for therapy. Although the definition was based on previous literature [11,13], a possible misclassification of prophylactic drugs as therapeutic or vice versa may result in individuals receiving preventive treatment to be incorrectly identified as having already experienced VTE. This may have a significant impact on establishing causality.

Furthermore, exposure variables were queried from the administrative database using SQL in DBeaver. However, only patients who were exposed to any anti-diabetic drug at any time from 2018 to 2020 were queried, without looking at temporality, or if the exposure happened before the event. Another exposure variable for every drug was then made in R with the full cohort database containing all variables. Since we used the event date (VTE date) of the cases as the sampling date for the controls after having done the matching, which allowed for the controls to have a correct exposure status variable (exposure to each drug before the sampling date), we are not able to provide a crude estimate of the odds ratio before matching, as there was no exposure variable (with temporality) before doing the matching. This would have been important to do, to see how much potential bias the matching introduced.

The study period (period where exposed and unexposed cases and controls are sampled from for the analysis) was defined as 2019 to 2020. This was based on the assumption that the SNDS database has information on diabetic patients from 2016 to 2020, and to ensure sufficient time for those diabetic patients to have taken anti-diabetic drugs when estimating the risk of VTE by the type of anti-diabetic drugs. Since there was no prescription of anti-diabetic drugs in the first two years (2016 and 2017), it was necessary to extend the source population recruitment period (cohort of diabetics) from 2016-2017 to 2016-2018. This only left two years (2019 and 2020) to recruit patients from the cohort of diabetics into the study population by looking at their outcome. This also meant less time to assess exposure status, which in turn reduced the sample size of exposed and unexposed to certain drugs among cases and controls and the power to detect differences in effect measure for the drugs alpha-glucosidase inhibitors and DPP-4 inhibitors.

Conclusion

In conclusion, the study found that use of biguanides was associated with higher odds of VTE, while use of alpha glucosidase inhibitors and sulfonylureas was associated with lower odds of VTE. Use of DPP-4 inhibitors was not associated with higher or lower odds of VTE. However, the presence of potential bias, the fact that these results contradict previous studies and the lack of generalizability means these results should be interpreted with caution. Further investigation is warranted on whether these anti-diabetic medications have a protective or harmful effect on the risk of VTE, as well as determining if these results are present in the general population.

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Appendix 1: Variables operationalization

Source Population

Variable Name	Variable Definition	Table	Query
HOSP_MAIN_DGN	Main diagnosis (ICD10)	TAB_HOSPITALISATION	E11% - Type 2 DM
LTI_ICD_REASON	Medical Reason or Pathology (ICD10)	TAB_LONG_TERM_ILLNESS	E11% - Type 2 DM
DGN_ASS	Associated Diagnosis (ICD10)	TAB_MSO_ASS_DGN	E11% - Type 2 DM
DRUG_ATC_C07	ATC Code Related to this Drug	THS_DRUGS	A10A% - Insulin A10B% - Blood Glucose Lowering Drugs excl. Insulin except A10BX06

Exposure

Variable Name	Variable Definition	Table	Query
DRUG_ATC_C07	ATC Code Related to this Drug	THS_DRUGS	A10B% - Blood Glucose Lowering Drugs excl. Insulin A10BA% Biguanides A10BB% - Sulfonylureas A10BF% - Alpha-glucosidase Inhibitors A10BH% - DPP-4 Inhibitors A10BJ% - GLP-1 Analogues A10BK% - SGLT2 Inhibitors A10A% - Insulins and Analogues

Outcome

Variable Name	Variable Definition	Table	Query
HOSP_MAIN_DGN	Main Diagnosis (ICD10)	TAB_HOSPITALISATION	I26% - Pulmonary Embolism I80% - Phlebitis and thrombophlebitis I82% - Other venous embolism or thrombosis
DGN_ASS	Associated Diagnosis (ICD10)	TAB_MSO_ASS_DGN	I26% - Pulmonary Embolism I80% - Phlebitis and thrombophlebitis I82% - Other venous embolism or thrombosis
PROC_COD	Procedure Code (CCAM)	TAB_MSO_PROCEDURES	DHNF001 - Venous Thrombolysis EGFA004 - Venous Thrombectomy
DRUG_ATC_C07	ATC Code Related to this Drug		B01AB% - Low-molecular-weight Heparin AND

DRUG_NAME	Trade name of the drug	THS_DRUGS	*Exclude Drug_Name lovenox 2%, INNOHEP 4%, INNOHEP 3%, INNOHEP 2%

*excluding the heparin drugs with a dosage lower than 5000 UI on average (which are not therapeutic for VTE but used for prophylaxis of VTE) (11)

Covariates

Covariate name	Variable name	Table	Query
Age		TAB_PATIENT	Diabetes diagnosis date* - PAT_BIRTH_DATE
Sex		TAB_PATIENT	PAT_SEX_COD
Fracture (any)		TAB_HOSPITALIZATION	S12% S22% S32% S42% S52% S62% S72% S82% S92% T02% T08% T10% T12% T142%
Hypertension		TAB_HOSPITALIZATION OR TAB_LONG_TERM_ILLNESS OR TAB_MSO_ASS_DGN	I10% I11% I12% I13% I14% I15%
Cancer		TAB_HOSPITALIZATION OR TAB_LONG_TERM_ILLNESS OR TAB_MSO_ASS_DGN	C%
Chronic obstructive pulmonary disease (COPD)		TAB_HOSPITALIZATION OR TAB_LONG_TERM_ILLNESS OR TAB_MSO_ASS_DGN	J40% J44%

Cardiothoracic, abdominal, pelvic or orthopedic surgery surgery		TAB_PRS_PROCEDURES OR TAB_MSO_PROCEDURES	**substring**(PROC_COD,1,2) **in** ('DA','DB','DC','DD','DE','DF','DG','DH','DK','DZ','GF','GG','GH','HF','HG','HH','HJ','HL','HM','HN','HP','JA','JD','JF','LE','LF','LH','LJ','NA','NB','NC','ND','NE','NF','NG','ZB','ZC','ZE') **and** **substring**(PROC_COD,4,1)='A' first: codes for major anatomical device + organ (i.e. Pericardium DC Coronary arteries DD Heart excitation conduction system DE Pulmonary vessels DF Aorta DG Vena cava DH Cardiac motricity DK Whole heart, heart and large vessels, unspecified DZ Lungs GF Greaves GG Mediastinal space GH Stomach HF Small intestine HG Colon and appendix HH Rectum HJ Liver HL Bladder and bile ducts HM Pancreas and pancreatic ducts HN Peritoneum and peritoneal cavity HP Kidney JA Bladder, urachus JD Retroperitoneal and subperitoneal space JF Thoracic spine, thoracolumbar hinge LE Lumbar spine, lumbosacral hinge LF Spine, unspecified LH Thoracic cage LJ Coxal bone NA Femur and patella NB Leg bones NC

			Foot bone ND Pelvic girdle joints, coxofemoral joint NE Knee joint NF Ankle joints NG Thorax ZB Abdomen and pelvis ZC Lower limb ZE) second: approach or technique (i.e. surgery)

* Defined as either the hospitalization start date, the long term disease start date, or the prescription date

Appendix 2: Results of Sensitivity Analysis

	Matched & Crude Model			Matched & Adjusted Model*		
Antidiabetic Medication	**OR**[1]	**95% CI**[1]	**p-value**	**OR**[1]	**95% CI**[1]	**p-value**
Biguanides						
0	—	—		—	—	
1	1.28	1.15, 1.43	<0.001	1.20	1.07, 1.34	0.002
Alpha glucosidase inhibitors						
0	—	—		—	—	
1	0.29	0.07, 0.82	0.043	0.40	0.09, 1.13	0.13
Dipeptidyl peptidase 4 (DPP-4) inhibitors						
0	—	—		—	—	
1	0.95	0.49, 1.72	0.9	0.88	0.44, 1.65	0.7
Sulfonylureas						
0	—	—		—	—	
1	0.59	0.47, 0.74	<0.001	0.70	0.56, 0.88	0.002

[1] OR = Odds Ratio, CI = Confidence Interval

*Adjusted on matching variables of age, sex, cancer, COPD, hypertension, fracture, and surgery.